

SEQUENCE LISTING

<110> Takeda Pharmaceutical Company Limited

<120> Metastin Derivatives And Its Use

<130> G05-0018

<150> PCT/JP2003/016978

<151> 2003-12-26

<150> JP 2002-377179

<151> 2002-12-26

<160> 22

<210> 1

<211> 54

<212> PRT

<213> Homo sapiens

<400> 1

Gly Thr Ser Leu Ser Pro Pro Pro Glu Ser Ser Gly Ser Arg Gln Gln

1 5 10 15

Pro Gly Leu Ser Ala Pro His Ser Arg Gln Ile Pro Ala Pro Gln Gly

20 25 30

Ala Val Leu Val Gln Arg Glu Lys Asp Leu Pro Asn Tyr Asn Trp Asn

35 40 45

Ser Phe Gly Leu Arg Phe

50

<210> 2

<211> 162

<212> DNA

<213> Homo sapiens

<400> 2

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ggtactttctc tgttccgcc gccggaatct tctggttctc gtcagcagcc ggtctgtct 60
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gacctgccga actacaactg gaactctttc ggtctgcgtt tc 162

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<210> 3

<211> 152

<212> PRT

<213> Mus musculus

<400> 3

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Met Tyr Leu Arg Phe Gly Val Asp Val Cys Ser Leu Ser Pro Trp Lys
      5              10              15
Glu Thr Val Asp Leu Pro Leu Pro Pro Arg Met Ile Ser Met Ala Ser
      20              25              30
Trp Gln Leu Leu Leu Leu Cys Val Ala Thr Tyr Gly Glu Pro Leu
      35              40              45
Ala Lys Val Ala Pro Gly Ser Thr Gly Gln Gln Ser Gly Pro Gln Glu
      50              55              60
Leu Val Asn Ala Trp Glu Lys Glu Ser Arg Tyr Ala Glu Ser Lys Pro
      65              70              75              80
Gly Ser Ala Gly Leu Arg Ala Arg Arg Ser Ser Pro Cys Pro Pro Val
      85              90              95
Glu Gly Pro Ala Gly Arg Gln Arg Pro Leu Cys Ala Ser Arg Ser Arg
      100             105             110
Leu Ile Pro Ala Pro Arg Gly Ala Val Leu Val Gln Arg Glu Lys Asp
      115             120             125
Leu Ser Thr Tyr Asn Trp Asn Ser Phe Gly Leu Arg Tyr Gly Arg Arg
      130             135             140
Gln Ala Ala Arg Ala Ala Arg Gly
145              150

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<210> 4

<211> 456

<212> DNA

<213> Mus musculus

<400> 4

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 gtcgccacct atggggagcc gctggcaaaa gtgaagcctg gatccacagg ccagcagtcc 180
 ggaccccagg aactcgttaa tgcctgggaa aaggaatcgc ggtatgcaga gagcaagcct 240
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 gggcgccagc ggcccctgtg tgcctccgc agtcgcctga tccctgcgcc ccgcggagcg 360
 gtgctggtgc agcgggagaa ggacctgtcc acctacaact ggaactcctt cggcctgcgc 420
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<210> 5

<211> 156

<212> PRT

<213> Mus musculus

<400> 5

Met	Tyr	Leu	Arg	Phe	Gly	Val	Asp	Val	Cys	Ser	Leu	Ser	Pro	Trp	Lys
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Glu	Thr	Val	Asp	Leu	Pro	Leu	Pro	Pro	Arg	Met	Ile	Ser	Met	Ala	Ser
				20					25					30	
Trp	Gln	Leu	Leu	Leu	Leu	Leu	Cys	Val	Ala	Thr	Tyr	Gly	Glu	Pro	Leu
				35					40					45	
Ala	Lys	Val	Ala	Pro	Leu	Val	Lys	Pro	Gly	Ser	Thr	Gly	Gln	Gln	Ser
				50					55					60	
Gly	Pro	Gln	Glu	Leu	Val	Asn	Ala	Trp	Glu	Lys	Glu	Ser	Arg	Tyr	Ala
				65					70					75	
Glu	Ser	Lys	Pro	Gly	Ser	Ala	Gly	Leu	Arg	Ala	Arg	Arg	Ser	Ser	Pro
									85					90	
Cys	Pro	Pro	Val	Glu	Gly	Pro	Ala	Gly	Arg	Gln	Arg	Pro	Leu	Cys	Ala
				100					105					110	
Ser	Arg	Ser	Arg	Leu	Ile	Pro	Ala	Pro	Arg	Gly	Ala	Val	Leu	Val	Gln
				115					120					125	
Arg	Glu	Lys	Asp	Leu	Ser	Thr	Tyr	Asn	Trp	Asn	Ser	Phe	Gly	Leu	Arg
				130					135					140	
Tyr	Gly	Arg	Arg	Gln	Ala	Ala	Arg	Ala	Ala	Arg	Gly				
				145					150					155	

<210> 6

<211> 468

<212> DNA

<213> *Mus musculus*

<400> 6

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gtcgccacct atggggagcc gctggcaaaa gtggcacctt tggatgaagcc tggatccaca  180
ggccagcagt cgggacccca ggaactcgtt aatgcctggg aaaaggaatc gcggtatgca  240
gagagcaagc ctgggtctgc agggctgcgc gctcgtaggt cgtcgccatg cccgccggtt  300
gagggccccg cggggcgcca gcggcccctg tgtgcctccc gcagtcgcct gatccctgcg  360
ccccgcggag cgggtctggt gcagcgggag aaggacctgt ccacctacaa ctggaactcc  420
ttcggcctgc gctacggcag gaggcaggcg gcgcgggcag cacggggc   468

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<210> 7

<211> 130

<212> PRT

<213> *Rattus sp.*

<400> 7

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Met Thr Ser Leu Ala Ser Trp Gln Leu Leu Leu Leu Cys Val Ala
      5              10              15
Ser Phe Gly Glu Pro Leu Ala Lys Met Ala Pro Val Val Asn Pro Glu
      20              25              30
Pro Thr Gly Gln Gln Ser Gly Pro Gln Glu Leu Val Asn Ala Trp Gln
      35              40              45
Lys Gly Pro Arg Tyr Ala Glu Ser Lys Pro Gly Ala Ala Gly Leu Arg
      50              55              60
Ala Arg Arg Thr Ser Pro Cys Pro Pro Val Glu Asn Pro Thr Gly His
      65              70              75              80
Gln Arg Pro Pro Cys Ala Thr Arg Ser Arg Leu Ile Pro Ala Pro Arg
      85              90              95
Gly Ser Val Leu Val Gln Arg Glu Lys Asp Met Ser Ala Tyr Asn Trp
      100             105             110
Asn Ser Phe Gly Leu Arg Tyr Gly Arg Arg Gln Val Ala Arg Ala Ala
      115             120             125
Arg Gly

```

130

<210> 8

<211> 390

<212> DNA

<213> Rattus sp.

<400> 8

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caggaaactcg ttaatgcctg gcaaaagggc ccgcggtatg cagagagcaa gcctggggct 180
gcaggactgc gcgctcgccg aacatcgcca tgcgcgccgg tggagaaccc cacggggcac 240
cagcggccccc cgtgtgccac ccgcagtcgc ctgacccctg cgccccgcgg atcggtgctg 300
gtgcagcgcg agaaggacat gtcagcctac aactggaact cctttggcct gcgctacggc 360
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<210> 9

<211> 398

<212> PRT

<213> Homo sapiens

<400> 9

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Met His Thr Val Ala Thr Ser Gly Pro Asn Ala Ser Trp Gly Ala Pro
          5              10              15
Ala Asn Ala Ser Gly Cys Pro Gly Cys Gly Ala Asn Ala Ser Asp Gly
          20              25              30
Pro Val Pro Ser Pro Arg Ala Val Asp Ala Trp Leu Val Pro Leu Phe
          35              40              45
Phe Ala Ala Leu Met Leu Leu Gly Leu Val Gly Asn Ser Leu Val Ile
          50              55              60
Tyr Val Ile Cys Arg His Lys Pro Met Arg Thr Val Thr Asn Phe Tyr
          65              70              75              80
Ile Ala Asn Leu Ala Ala Thr Asp Val Thr Phe Leu Leu Cys Cys Val
          85              90              95
Pro Phe Thr Ala Leu Leu Tyr Pro Leu Pro Gly Trp Val Leu Gly Asp
          100             105             110
Phe Met Cys Lys Phe Val Asn Tyr Ile Gln Gln Val Ser Val Gln Ala

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115	120	125
Thr Cys Ala Thr Leu Thr Ala Met Ser Val Asp Arg Trp Tyr Val Thr		
130	135	140
Val Phe Pro Leu Arg Ala Leu His Arg Arg Thr Pro Arg Leu Ala Leu		
145	150	155
Ala Val Ser Leu Ser Ile Trp Val Gly Ser Ala Ala Val Ser Ala Pro		
165	170	175
Val Leu Ala Leu His Arg Leu Ser Pro Gly Pro Arg Ala Tyr Cys Ser		
180	185	190
Glu Ala Phe Pro Ser Arg Ala Leu Glu Arg Ala Phe Ala Leu Tyr Asn		
195	200	205
Leu Leu Ala Leu Tyr Leu Leu Pro Leu Leu Ala Thr Cys Ala Cys Tyr		
210	215	220
Ala Ala Met Leu Arg His Leu Gly Arg Val Ala Val Arg Pro Ala Pro		
225	230	235
Ala Asp Ser Ala Leu Gln Gly Gln Val Leu Ala Glu Arg Ala Gly Ala		
245	250	255
Val Arg Ala Lys Val Ser Arg Leu Val Ala Ala Val Val Leu Leu Phe		
260	265	270
Ala Ala Cys Trp Gly Pro Ile Gln Leu Phe Leu Val Leu Gln Ala Leu		
275	280	285
Gly Pro Ala Gly Ser Trp His Pro Arg Ser Tyr Ala Ala Tyr Ala Leu		
290	295	300
Lys Thr Trp Ala His Cys Met Ser Tyr Ser Asn Ser Ala Leu Asn Pro		
305	310	315
Leu Leu Tyr Ala Phe Leu Gly Ser His Phe Arg Gln Ala Phe Arg Arg		
325	330	335
Val Cys Pro Cys Ala Pro Arg Arg Pro Arg Arg Pro Arg Arg Pro Gly		
340	345	350
Pro Ser Asp Pro Ala Ala Pro His Ala Glu Leu His Arg Leu Gly Ser		
355	360	365
His Pro Ala Pro Ala Arg Ala Gln Lys Pro Gly Ser Ser Gly Leu Ala		
370	375	380
Ala Arg Gly Leu Cys Val Leu Gly Glu Asp Asn Ala Pro Leu		
385	390	395

<211> 1194

<212> DNA

<213> Homo sapiens

<400> 10

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atgcacaccg tggctacgtc cggacccaac gcgtcctggg gggcaccggc caacgcctcc   60
ggctgcccgg gctgtggcgc caacgcctcg gacggcccag tcccttcgcc gcgggcccgtg  120
gacgcctggc tcgtgccgct cttcttcgcg gcgctgatgc tgctgggcct ggtggggaac  180
tcgctggtca tctacgtcat ctgccgccac aagccgatgc ggaccgtgac caacttctac  240
atgcceaacc tggcggccac ggacgtgacc ttctctctgt gctgcgtccc cttcacggcc  300
ctgctgtacc cgctgcccgg ctgggtgctg ggcgacttca tgtgcaagtt cgtcaactac  360
atccagcagg tctcgggtga ggccacgtgt gccactctga ccgccatgag tgtggaccgc  420
tggtacgtga cgggtgttccc gttgcgcgcc ctgcaccgcc gcacgccccg cctggcgcgtg  480
gctgtcagcc tcagcatctg ggtaggctct gcggcggtgt ctgcgccggt gctcgccctg  540
caccgcctgt caccggggcc gcgcgcctac tgcagtgagg ccttccccag ccgcgccctg  600
gagcgcgcct tcgcactgta caacctgctg gcgctgtacc tgctgccgct gctcgccacc  660
tgcgctgct atgcggccat gctgcgccac ctgggcccgg tcgccgtgcg ccccgcgccc  720
gccgatagcg cctgcaggg gcaggtgctg gcagagcgcg caggcgccgt gcgggccaag  780
gtctcgcggc tgggtggcggc cgtggtcctg ctcttcgccg cctgctgggg ccccatccag  840
ctgttcctgg tgtgcaggc gctgggcccc gcgggctcct ggcacccacg cagctacgcc  900
gcctacgcgc ttaagacctg ggctcactgc atgtcctaca gcaactccgc gctgaacccg  960
ctgctctacg ccttcctggg ctgcacttc cgacaggcct tccgccgct ctgcccctgc 1020
gcgccgcgcc gccccgcgc cccccgccg cccggaccct cggacccgc agccccacac 1080
gcggagctgc accgcctggg gtcccacccg gccccgccca gggcgagaa gccagggagc 1140
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<210> 11

<211> 396

<212> PRT

<213> Rattus sp.

<400> 11

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Met Ala Ala Glu Ala Thr Leu Gly Pro Asn Val Ser Trp Trp Ala Pro
      5              10              15
Ser Asn Ala Ser Gly Cys Pro Gly Cys Gly Val Asn Ala Ser Asp Gly
      20              25              30
Pro Gly Ser Ala Pro Arg Pro Leu Asp Ala Trp Leu Val Pro Leu Phe

```

35	40	45
Phe Ala Ala Leu Met Leu Leu Gly Leu Val Gly Asn Ser Leu Val Ile		
50	55	60
Phe Val Ile Cys Arg His Lys His Met Gln Thr Val Thr Asn Phe Tyr		
65	70	75
Ile Ala Asn Leu Ala Ala Thr Asp Val Thr Phe Leu Leu Cys Cys Val		
85	90	95
Pro Phe Thr Ala Leu Leu Tyr Pro Leu Pro Thr Trp Val Leu Gly Asp		
100	105	110
Phe Met Cys Lys Phe Val Asn Tyr Ile Gln Gln Val Ser Val Gln Ala		
115	120	125
Thr Cys Ala Thr Leu Thr Ala Met Ser Val Asp Arg Trp Tyr Val Thr		
130	135	140
Val Phe Pro Leu Arg Ala Leu His Arg Arg Thr Pro Arg Leu Ala Leu		
145	150	155
Thr Val Ser Leu Ser Ile Trp Val Gly Ser Ala Ala Val Ser Ala Pro		
165	170	175
Val Leu Ala Leu His Arg Leu Ser Pro Gly Pro His Thr Tyr Cys Ser		
180	185	190
Glu Ala Phe Pro Ser Arg Ala Leu Glu Arg Ala Phe Ala Leu Tyr Asn		
195	200	205
Leu Leu Ala Leu Tyr Leu Leu Pro Leu Leu Ala Thr Cys Ala Cys Tyr		
210	215	220
Gly Ala Met Leu Arg His Leu Gly Arg Ala Ala Val Arg Pro Ala Pro		
225	230	235
Thr Asp Gly Ala Leu Gln Gly Gln Leu Leu Ala Gln Arg Ala Gly Ala		
245	250	255
Val Arg Thr Lys Val Ser Arg Leu Val Ala Ala Val Val Leu Leu Phe		
260	265	270
Ala Ala Cys Trp Gly Pro Ile Gln Leu Phe Leu Val Leu Gln Ala Leu		
275	280	285
Gly Pro Ser Gly Ala Trp His Pro Arg Ser Tyr Ala Ala Tyr Ala Leu		
290	295	300
Lys Ile Trp Ala His Cys Met Ser Tyr Ser Asn Ser Ala Leu Asn Pro		
305	310	315
Leu Leu Tyr Ala Phe Leu Gly Ser His Phe Arg Gln Ala Phe Cys Arg		
325	330	335

Val Cys Pro Cys Gly Pro Gln Arg Gln Arg Arg Pro His Ala Ser Ala
 340 345 350
 His Ser Asp Arg Ala Ala Pro His Ser Val Pro His Ser Arg Ala Ala
 355 360 365
 His Pro Val Arg Val Arg Thr Pro Glu Pro Gly Asn Pro Val Val Arg
 370 375 380
 Ser Pro Ser Val Gln Asp Glu His Thr Ala Pro Leu
 385 390 395

<210> 12

<211> 1188

<212> DNA

<213> Rattus sp.

<400> 12

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gatgcctggc tgggtcccct gtttttcgct gccctaattgt tgcctgggct agtcgggaac    180
tactgggtca tcttcgttat ctgccgccac aagcacatgc agaccgtcac caatttctac    240
atcgctaacc tggcgggccac agatgtcact ttccttctgt gctgcgtacc cttcaccgcg    300
ctcctctatc cgctgcccac ctgggtgctg ggagacttca tgtgcaaatt cgtcaactac    360
atccagcagg tctcggtgca agccacatgt gccactttga cagccatgag tgtggaccgc    420
tggtacgtga ctgtgttccc gctgcgtgca cttcaccgcc gactccgcg cctggccctg    480
actgtcagcc ttagcatctg ggtgggttcc gcagctgitt ccgccccggt gctggctctg    540
caccgcctgt cgcccgggcc tcacacctac tgcagtgagg cgtttcccag ccgtgccctg    600
gagcgcgctt tcgcgtcta caacctgctg gccctatacc tgcctgcgt gctcgccacc    660
tgcgcctgct acggtgccat gctgcgccac ctgggccgcg ccgctgtacg ccccgcaccc    720
actgatggcg ccctgcaggg gcagctgcta gcacagcgcg ctggagcagt gcgcaccaag    780
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gcctacgcgc tcaagatctg ggctcactgc atgtcctaca gcaattctgc gctcaacccg    960
ctgctctatg ccttcttggg ttcaccattc agacaggcct tctgccggt gtgcccctgc   1020
ggcccgcaac gccagcgtcg gcccacgcg tcagcgcact cggaccgagc cgcaccccat   1080
agtgtgccgc acagccgggc tgcgcaccct gtccgggtca ggacccccga gcctgggaac   1140
cctgtggtgc gctcgccctc tgttcaggat gaacacactg ccccactc    1188

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<210> 13

<211> 396

<212> PRT

<213> Mus musculus

<400> 13

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Met Ala Thr Glu Ala Thr Leu Ala Pro Asn Val Thr Trp Trp Ala Pro
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Ser Asn Ala Ser Gly Cys Pro Gly Cys Gly Val Asn Ala Ser Asp Asp
      20           25           30
Pro Gly Ser Ala Pro Arg Pro Leu Asp Ala Trp Leu Val Pro Leu Phe
      35           40           45
Phe Ala Thr Leu Met Leu Leu Gly Leu Val Gly Asn Ser Leu Val Ile
      50           55           60
Tyr Val Ile Cys Arg His Lys His Met Gln Thr Val Thr Asn Phe Tyr
65           70           75           80
Ile Ala Asn Leu Ala Ala Thr Asp Val Thr Phe Leu Leu Cys Cys Val
      85           90           95
Pro Phe Thr Ala Leu Leu Tyr Pro Leu Pro Ala Trp Val Leu Gly Asp
      100          105          110
Phe Met Cys Lys Phe Val Asn Tyr Ile Gln Gln Val Ser Val Gln Ala
      115          120          125
Thr Cys Ala Thr Leu Thr Ala Met Ser Val Asp Arg Trp Tyr Val Thr
      130          135          140
Val Phe Pro Leu Arg Ala Leu His Arg Arg Thr Pro Arg Leu Ala Leu
145          150          155          160
Ala Val Ser Leu Ser Ile Trp Val Gly Ser Ala Ala Val Ser Ala Pro
      165          170          175
Val Leu Ala Leu His Arg Leu Ser Pro Gly Pro Arg Thr Tyr Cys Ser
      180          185          190
Glu Ala Phe Pro Ser Arg Ala Leu Glu Arg Ala Phe Ala Leu Tyr Asn
      195          200          205
Leu Leu Ala Leu Tyr Leu Leu Pro Leu Leu Ala Thr Cys Ala Cys Tyr
      210          215          220
Gly Ala Met Leu Arg His Leu Gly Arg Ala Ala Val Arg Pro Ala Pro
225          230          235          240
Thr Asp Gly Ala Leu Gln Gly Gln Leu Leu Ala Gln Arg Ala Gly Ala
      245          250          255

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Val Arg Thr Lys Val Ser Arg Leu Val Ala Ala Val Val Leu Leu Phe
 260 265 270
 Ala Ala Cys Trp Gly Pro Ile Gln Leu Phe Leu Val Leu Gln Ala Leu
 275 280 285
 Gly Pro Ser Gly Ala Trp His Pro Arg Ser Tyr Ala Ala Tyr Ala Val
 290 295 300
 Lys Ile Trp Ala His Cys Met Ser Tyr Ser Asn Ser Ala Leu Asn Pro
 305 310 315 320
 Leu Leu Tyr Ala Phe Leu Gly Ser His Phe Arg Gln Ala Phe Cys Arg
 325 330 335
 Val Cys Pro Cys Cys Arg Gln Arg Gln Arg Arg Pro His Thr Ser Ala
 340 345 350
 His Ser Asp Arg Ala Ala Thr His Thr Val Pro His Ser Arg Ala Ala
 355 360 365
 His Pro Val Arg Ile Arg Ser Pro Glu Pro Gly Asn Pro Val Val Arg
 370 375 380
 Ser Pro Cys Ala Gln Ser Glu Arg Thr Ala Ser Leu
 385 390 395

<210> 14

<211> 1188

<212> DNA

<213> Mus musculus

<400> 14

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 gatgcctggc tggttcccct gtttttcgct aactcatgt tgcttgggct ggtcggaaac 180
 tcatttgtca tctacgttat ctgccgccac aagcacatgc agacagttac caacttctac 240
 atcgctaacc tggctgccac agacgtcact ttcctactgt gctgcgtgcc cttaccgca 300
 ctctctacc cgctgccgc ctgggtgctg ggagacttca tgtgcaaatt cgtcaactac 360
 atccagcagg tctcggtgca agccacatgt gccactctga cggccatgag tgtggaccgc 420
 tggatatgta ctgtgttccc gctgcgtgca cttaccgcc gactccgcg cctggccctg 480
 gctgtcagcc tcagcatctg ggtgggggtca gcagctgtgt cgcgccgggt gctggccctg 540
 caccgcctgt cgccagggcc tcgcacctac tgcagcgagg cgtttccag ccgcgccctg 600
 gagcgcgcct tcgcgtcta caacctgctg gctctatata tgctgccgct gctgccacc 660
 tgcgcctgct acggcgccat gctgcgccac ctgggcccgtg cggctgtacg ccccgaccc 720

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actgacggcg ccctgcaggg acagctgcta gcacagcgcg ccggagcagt gcgcaccaag 780
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ctgttccttg tgcttcaagc cctggggccc tcgggggcct ggacacctcg aagctatgcc 900
gcctacgcgg tcaagatctg ggctcactgc atgtcctaca gcaactcggc gctcaatccg 960
ctgctctatg ccttcctggg ttcacacttc agacaggcct tctgccgct gtgcccctgc 1020
tgccggcaac gccagcgccg gccccacacg tcagcgcaact cggaccgagc tgcaactcac 1080
actgtgccgc acagccgtgc tgcgcaccct gtgcggatca ggagcccgga gcctgggaac 1140
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<210> 15

<211> 15

<212> PRT

<213> Artificial

<220>

<223> the C-terminus of the polypeptide is amide (-CONH₂) form

<400> 15

Lys Asp Leu Pro Asn Tyr Asn Trp Asn Ser Phe Gly Leu Arg Phe

1 5 10 15

<210> 16

<211> 10

<212> PRT

<213> Artificial

<220>

<223> the C-terminus of the polypeptide is amide (-CONH₂) form

<400> 16

Tyr Asn Trp Asn Ser Phe Gly Leu Arg Phe

1 5 10

<210> 17

<211> 9

<212> PRT

<213> Artificial

<220>

<223> the C-terminus of the polypeptide is amide (-CONH₂) form

<400> 17

Asn Trp Asn Ser Phe Gly Leu Arg Phe

1 5 9

<210> 18

<211> 8

<212> PRT

<213> Artificial

<220>

<223> the C-terminus of the polypeptide is amide (-CONH₂) form

<400> 18

Trp Asn Ser Phe Gly Leu Arg Phe

1 5 8

<210> 19

<211> 45

<212> DNA

<213> Homo sapiens

<400> 19

aaggacctgc cgaactacaa ctggaactcc ttcggcctgc gcttc

45

<210> 20

<211> 30

<212> DNA

<213> Homo sapiens

<400> 20

tacaactgga actccttcgg cctgcgcttc

30

<210> 21

<211> 27

<212> DNA

<213> Homo sapiens

<400> 21

aactggaact ccttcggcct gcgcttc

27

<210> 22

<211> 24

<212> DNA

<213> Homo sapiens

<400> 22

tggaactcct tcggcctgcg cttc

24